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Innovations

Boston Autism Consortium Searches for Genetic Clues to Autism's Puzzle

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Autism has received considerable attention in the past few years; some say its incidence is increasing. Upon closer examination, however, the picture blurs. A nascent initiative in Boston, the Boston Autism Consortium, may represent a pragmatic model for dealing with complex diseases, one that involves different institutions collaborating rather than competing and applying research directly to patient care.

Autism is a heterogeneous neurodevelopmental disorder. The canopy of autism actually covers a number of pervasive development disorders (referred to as "autism spectrum disorders") that vary in severity. Popular media accounts have asserted that autism is rising due to environmental triggers, but it may be a matter of shifting diagnosis criteria. For example, the CDC (www.cdc.gov) currently estimates that from 1 in 500 to 1 in 150 children is in some way autistic, depending on the definition and method of screening. Autism appears to affect the brain systemically and, in some cases, affects the body as well. The disorder strikes children across racial and ethnic lines, but affects boys four times as often as girls. In the absence of an organic biomarker, autism is diagnosed purely by impairment in communication and language development, as well as certain rigid and repetitive behaviors and preoccupations.

Many scientists are now focusing on genetic causes, perhaps involving combinations of dozens of genes. There are only 2–3 statistically significant findings linking autism to specific chromosomal loci. And it is thought by many researchers that patterns of gene expression, in response to as yet unknown environmental triggers, make certain individuals more likely to develop autism.

Some conceptualize autism not as a black and white condition, but rather in shades of grey; meaning that in an affected family, one should find different levels of autism ranging from benign to severe. Notably, a sibling of an autistic individual is more likely to have an autism-spectrum disorder compared to an unrelated person, although estimates for the likelihood vary. In the case of identical twins, different studies report anything from a 36 to 91 percent chance, depending on the screening method, that if one twin is autistic, the other will be as well. Essentially, nobody knows what the important genes are or how they code for the condition and interact with each other or with environmental triggers to translate into the disorder.

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The Spirit of Collaboration Means Actually Working Together in Practice

This paucity of concrete information provided the impetus for the launch of the Autism Consortium in Boston last year. Over 50 researchers drawn from various disciplines at 11 of Boston's powerhouse institutions, including Harvard, MIT, Tufts, the Broad Institute for Genetic Research, Massachusetts General Hospital, Boston University, Boston Children's Hospital, Beth Israel Deaconess Medical Center, as well as the Cambridge Healthcare Alliance, are collaborating to improve screening, standardize diagnostic protocols, efficiently translate laboratory results back to the clinic, and ultimately identify potential targets for therapies.

The consortium is primarily funded by private philanthropists, led by Paul Marcus, a MIT alumnus with an interest in developmental disabilities. Since the project's inception in 2006, Marcus and his foundation have recruited other donors and amassed between $10 and $15 million for research. With fewer federal funds available, the money provides an attractive inducement for competing institutions to collaborate. The consortium hopes to eventually apply for NIH funding as an entity, although currently researchers working within its framework continue to apply for individual and collaborative grants.

This pan-institutional endeavor is a pioneering one for the Boston biomedical community. The consortium is directed by an executive committee including Professor Mriganka Sur, head of the Department of Brain and Cognitive Science at MIT; Dr. Christopher Walsh, chief of the Division of Genetics at Childrens' Hospital Boston; and Dr. James Gusella, professor of neurogenetics at the Massachusetts General Center for Human Genetic Research. "This model is based on the concept that the study of human disease should be viewed as a cycle that begins and ends with patients and their families." said Gusella. "Ultimately autism is a really hard problem. No one scientist can do it alone."

The executive committee coordinates cross-institutional working groups in areas including cognitive neuroscience, clinical medicine, and bioinformatics. At the core of the project is the assembly of a large data set of phenotypes of measured behaviors and biological samples from patients and their families. The hope is that rigorous data analysis will reveal

new patterns that illuminate disease mechanisms and provide clues to potential interventions. The next phase is to obtain as many DNA samples as possible from autistic individuals and their family members, as certain working groups are focusing on discovering and characterizing autism-related genes.

Parsing Out the Nitty-Gritty Details

The Autism Consortium has launched the Autism Gene Discovery Project, which is combing the entire human genome for clues to the causes of autism. The Consortium is working with the Broad Institute on completing a whole genome association scan using data from close to 800 families from the Autism Genetic Research Exchange (AGRE) database.

Researchers are using the Affymetrix GeneChip Human Mapping 500K Array to screen more than 3,000 biological samples from the AGRE repository. According to Dr. Susan Santangelo, associate professor of psychiatry, Harvard Medical School, who is conducting gene mapping studies of autism, until fairly recently, genes were implicated by linkage analysis, which identifies regions of the genome that are shared more frequently than by chance among affected individuals. These techniques work best when the genetic contribution from any single gene is large. Now gene mapping studies rely much more heavily on association analyses, which are more powerful when the contribution of any given gene is small to moderate. These analyses also can better pinpoint the chromosomal locations of the genes involved. This technique has become more widely used as more appropriate genetic markers such as single nucleotide polymorphisms (SNPs) have become available thanks to the Human Genome Project. However, ''the entire AGRE collection does not yet have a large amount of phenotypic data on all the families,'' said Santangelo, ''Because this was begun several years ago, they mainly focused on the collection of diagnostic information. Most in the field now agree that diagnostic data alone are not going to get us there because we're dealing with very heterogeneous syndromes.''

Assembling Puzzle Pieces in Hopes of Finding a Pattern

The AGRE database was cofounded in 1997 under the auspices of the Cure Autism Now Foundation and a scientific steering committee chaired by Dr. Daniel Geschwind, who directs the Center for Autism Research and Treatment (CART) at UCLA. CART is collecting longitudinal information on sibling pairs, in which one sibling of an autistic patient is followed from infancy into early childhood. The AGRE database is now cofunded by NIMH and contains biomaterials from thousands of patients as well as clinical and psychological phenotype data such as language skills, IQ measurements, and medical information concerning patients and relatives. AGRE is used by 140 researchers around the world. ''It is not just about finding genes,'' said Geschwind. ''It is about finding genes, understanding how they cause autism or might contribute to autism susceptibility'' as well as ''how they relate to different subsets of autism, because we have really begun to think about autism as 'the autisms.' That is, autism is a syndrome with likely hundreds of distinct causes.''

Another data collection effort is underway at the MIND Institute at the University of California, Davis, headed by David Amaral, professor of medical psychiatry. Data is being collected on 1,500 patients over five years. MIND is also combining phenotype information with data on environmental toxins as well as looking for biomarkers.

In addition to drawing on the AGRE resources, the Autism Consortium is also collaborating with scientists at Johns Hopkins University, who are in the third year of an autism study using the 500K array to scan 600 families. The study is led by Professor Aravinda Chakravarti, director of the McKusick-Nathans Institute of Genetic Medicine, and is funded through the NIH.

Looking for the Larger Picture

The Learning and Developmental Disabilities Evaluation and Rehabilitation Services (LADDERS) program at Mass General Hospital is submitting data on 80 patients to the Autism Consortium in the first year of a two year collaboration. According to LADDERS director Dr. Margaret Bauman, the earlier children are diagnosed and put in treatment, the better they respond. Treatment can comprise intensive education, physical, speech, and language therapy and drugs. LADDERS also deals with the medical problems correlated to autism. Interestingly, Bauman's program looks for metabolic clues to serve as more precise ''fingerprints'' for the condition over behavioral observations. She emphasizes the importance of making families partners, rather than subjects, in ongoing research. ''You would want to hang on to your subjects once you have them.'' Bauman said. ''You don't want to make them feel like, pardon the expression, guinea pigs. You want them to feel like they are part of a larger picture.''

Getting Your Shirt on Straight

Researchers are in it for the long haul, but autism patients and their families have more immediate concerns. Mary Kae Marinac, a consultant north of Boston, has 12 year old, identical twin sons, ''happy, wonderful kids, both with autism.'' ''They tend to be what is considered on [the] lower end of the spectrum, in terms of communications and activities of daily living,'' said Marinac. ''They cannot read or write, they still struggle [with] whether a shirt is oriented frontwards or backwards, and only one is newly capable of wiping [after] bowel movements. They require extensive support.'' The twins attend a special school with a ratio of one staff member to every two students. ''Without extreme structure and rigidity in their day, they fall apart.'' said Marinac. For families like this, results from the Autism Consortium and other research efforts cannot come soon enough.

Ultimately, the Autism Consortium wants to find ways to improve the quality of life for people with autism. In the meantime, this collaborative effort may lead to prenatal diagnostics and to improved standards of care and support for patients and their families. But to decipher this puzzle, the first challenge is to find and then fit the scattered pieces together.

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